AF/ORF

PATENT
1422-0449P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Eiichi IISHI et al.	Conf.:	8402
Appl. No.:	09/697,329	Group:	1624
Filed:	October 27, 2000	Examiner:	HABTE, K.

For: ANHYDROUS MIRTAZAPINE CRYSTALS AND PROCESS FOR PREPARING THE SAME

LETTER ENCLOSING COMMUNICATION FROM FOREIGN PATENT OFFICE IN RELATED APPLICATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

March 4, 2005

Sir:

Enclosed herewith are copies of three (3) Notices of Opposition dated January 4, 2005, which were cited in connection with the corresponding European patent application.

Applicants note that three (3) of the references cited in the Notices have been already made of record. Specifically, US 4,062,848 was cited in the Information Disclosure Statement (IDS) filed on October 27, 2000. Kaspersen et al. was cited in the Office Action issued on February 14, 2001. WO 00/62782 corresponds to US 2003/069417, US 2003/088094, US 2003/0120068, and US 2003/135043, all of which were cited in the IDS filed on September 9, 2003.

Also, Applicants herewith enclose the documents cited in the three Notices. These documents include:

- Affidavit of Professor Michael B. Hursthouse;
- Experimental results for Example 6 of WO 00/62782;
- Experimental results for example bridging 1065 to 1066 of Kaspersen et al;
- Experimental results for step 4 of Example I of US 4,062,848;
- Experimental Report;
- Approval Letter for Remeron™ (Mirtazapine), Center for Drug Evaluation and Research, US Food and Drug Administration, June 14, 1996;
- "Environmental Impact Assessment Report for Remeron™", October 30, 1995, Pages 1, 2 and 11;
- DSC Results of Mirtazapine Products;
- Copy from database "Scifinder"; and
- Declaration of William De Wildt, Peter van Hoof, Catherine Crowley, and Peter Kirchholtes.

The Examiner is respectfully requested to make this letter and its enclosures of record and to consider all documents.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact **Garth M. Dahlen, Ph.D., Esq.** (Reg. No. 43,575)

at the below-listed number.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Gerald M. Murphy, Jr. #28,977

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/GMD/mua
1422-0449P

Attachment(s): Three communications relating to Notice of Opposition along with their attachments

R.N.

EPA/EPO/OEB
D-80298 München
+ 49 89 2399-0
TX 523 656 epmu d
FAX + 49 89 2399-4465

Europäisches Patentamt | European Patent Office | Office européen des brevets

Generaldirektion 2 | Directorate General 2 | Direction Générale 2

HOFFMANN - EITLE
Patent- und Rechtsanwälte
Arabellastrasse 4
81925 München
ALLEMAGNE

EINGEGANGEN
10. Jan. 2005
HOFFMANN • EITLE, MÜNCHEN
PATENTANWÄLTE RECHTSANWÄLTE

Datum/Date 04-01-2005

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
90731 a/fi	00962908.0-2117/1225174

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
Sumika Fine Chemicals Co., Ltd.

COMMUNICATION OF A NOTICE OF OPPOSITION

Enclosed herewith is a copy of a notice of opposition to the European patent specified above.

An invitation to file observations and to file amendments, where appropriate, to the description, claims and drawings (Rule 57(1) EPC) will be issued separately.

The period within which such observations may be filed will not be fixed until the following conditions are met:

(a) the opposition period has expired;

(b) the notice of opposition has been examined for certain formal requirements (Rule 56 EPC).

Formalities Officer
Tel. No.: (089) 2399- 7272

Enclosure: Notice of opposition

OIII Akzo Nobel N.V. fax and conf.

Printed: 03-01-2005 NEWOPPO 00962908

EPO - Munich
67

Notice of Opposition to a European Patent

21. Dez. 2004

To the European Patent Office

Tabulation marks

for EPO use only

I. Patent opposed

Opp. No. OPPO (1)

Patent No.	1 225 174
Application No.	00962908.0
Date of mention of the grant in the European Patent Bulletin (Art. 97(4), 99(1) EPC)	17.03.2004

Title of the invention:

Anhydrous mirtazapine crystals and process for the production thereof

II. Proprietor of the Patent

first named in the patent specification: SUMIKA FINE CHEMICALS Co., Ltd, Presently assigned to SUMITOMO

Opponent's or representative's reference (max. 15 spaces): Op.269 OREF

III. Opponent

OPPO (2)

Name / Address:

Akzo Nobel N.V.

Velperweg 76
6824 BM Arnhem
The Netherlands

State of residence or of principal place of business: The Netherlands

Telephone/Telex/Fax: +31 412 666 380 | | +31 412 650 592

Multiple opponents: ☐ further opponents see additional sheet

IV. Authorisation

1. Representative (Name only one representative to whom notification is to be made)

OPPO (9)

Name / Address of place of business:

P.M.G.F. van Wezenbeek
P.O. Box 20
5340 BH Oss
The Netherlands

Zur Kasse
A. 60,-

Telephone/Telex/Fax: +31 412 666 380 | | +31 412 650 592

Additional representative(s): ☒ (on additional sheet/see authorisation) OPPO (5)

2. Employee(s) of the opponent authorised for these opposition proceedings under Art. 133(3) EPC

Name(s):

Authorisation(s)

To 1./2.

☐ not considered necessary
☒ has/have been registered under No. 59
☐ is/are enclosed

for EPO use only

V. Opposition is filed against

— the patent as a whole [X]

— claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

— it is not new (Art. 52(1); 54 EPC) [X]

— it does not involve an inventive step (Art. 52(1); 56 EPC) [X]

— patentability is excluded on other grounds, i. e. Art. [ ]

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). [ ]

(c) the subject-matter of the patent opposed extends beyond the content of the application/ of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). [ ]

VII. Facts and arguments

(Rule 55(c) EPC)
presented in support of the opposition are submitted herewith on a separate sheet (annex 1) [X]

VIII. Other requests:

Oral proceedings are requested under Art 116(1) EPC in case the opposition division intends to maintain the patent as it is or in amended form

IX. Evidence presented

for EPO use only

Enclosed = X

will be filed at a later date =

A. **Publications:** | Publication date

1 Kaspersen et al., The synthesis of Org 3770 labelled with 3H, 13Cand 14 C; Journal of labelled ompounds and Radiopharmaceuticals Vol XXVII, No 9 pp 1056-1068, 1989

Particular relevance (page, column, line, fig.):
p 1066, top paragraph

2 Printed pages from database Scifinder for names of mirtazapine and formula

Particular relevance (page, column, line, fig.):

3

Particular relevance (page, column, line, fig.):

4

Particular relevance (page, column, line, fig.):

5

Particular relevance (page, column, line, fig.):

6

Particular relevance (page, column, line, fig.):

7

Particular relevance (page, column, line, fig.):

Continued on additional sheet ☐

B. **Other evidence**

Declarations of De Wildt, van Hoof, Crowley and Kirchholtes.
To be submitted: Copies of invoices and declaration of Reijnierse

Continued on additional sheet ☐

X. Payment of the opposition fee is made

for EPO use only

[x] as indicated in the enclosed voucher for payment of fees and costs (EPO Form 1010)

[ ]

XI. List of documents

Enclosure No.		No. of copies	
0	[x] Form for notice of opposition	2 (min. 2)	
1	[x] Facts and arguments (see VII.)	2 (min. 2)	
2	Copies of documents presented as evidence (see IX.)		
2a	[x] — Publications	2 (min. 2 of each)	
2b	[x] — Other documents	2 (min. 2 of each)	
3	[ ] Signed authorisation(s) (see IV.)		
4	[x] Voucher for payment of fees and costs (see X.)	1	
5	[ ] Cheque		
6	[ ] Additional sheet(s)	(min. 2 of each)	
7	[ ] Other (please specify here):		

XII. Signature of opponent or representative

Place Oss

Date 17 December 2004

Please type name under signature. In the case of legal persons, the position which the person signing holds within the company should also be typed.

ADDITIONAL SHEET

Additional Representatives:

H. Kraak

P.M.G.F. van Wezenbeek

M. Hogenbirk

L.A.G.M. van den Broek

All residing at:

P.O. Box 20
5340 BH OSS
The Netherlands

All authorized under G.A. No. 59

1. Indication of facts and evidence

The following documents have been used:

D1: Kaspersen, Van Rooij, Sperling and Wieringa, J. Labelled Compounds and Radiopharmaceuticals Vol XXVII pp 1055-1068.

D2: Copy from database "Scifinder"

D3-D7: Evidence is submitted for the prior sale of product by N.V. Organon, Oss of medicine containing mirtazapine according to claim 7. With invoices, copies of which will be submitted it is demonstrated that mirtazapine was sold in 30 mg tablets to clients of Organon before the earliest date of priority of the opposed patent. The affidavit of Crowley identifies the batch numbers which enable to trace the mirtazapine in the tablets back to production batch numbers. The declaration of Reijniers (will be submitted) identifies production methods used to produce this mirtazapine. The declaration of Kirchholtes testifies that those methods are substantially the same as the methods used today and as far as there were changes in the production procedures, these could not have resulted in a change in water content or crystal structure of the mirtazapine product. The product produced and supplied up to the present by Organon is containing about 2.5% water, is dry and crystalline and has the X-ray diffraction pattern according to the hydrate claimed in claim 7 of the opposed patent.

D3: Declaration of William De Wildt

D4: Declaration of Peter van Hoof

D5: Declaration of Catherine Crowley

D6: Declaration of Peter Kirchholtes

D6: Declaration of Ivan Reijniers (Will be submitted)

D7: Copies of invoices for deliveries in the year 1999 (Will be submitted)

2. Indication of the arguments

2.1 Claim 1 lacks inventive step (Art 56)

Mirtazapine is a well known drug used for the treatment of depression in medicines with trade names such as Remeron™ and Zispin™ (See D2). It is available as such since 1995 in European countries. The form of mirtazapine in Remeron is a dried water-containing crystalline form of mirtazapine. Available mirtazapine is the closest prior art. The distinguishing feature in claim 1 is that the claimed mirtazapine is an anhydrate with similar reduced (or non-)hygroscopic properties. The objective problem is to provide an alternative to available non-hygroscopic mirtazapine.

Opponent submits that it was well-known before the earliest priority date that compounds can occur in different crystalline forms and as solvates. Such forms may occur in one or in a plurality of crystalline forms. Such polymorphous forms can be used as alternative forms to available forms. The anhydrate defined in claim 1 is described in the opposed patent to be a form with lesser hygroscopic properties than another anhydrate form. It is not a technical achievement to discover that one anhydrate form is less hygroscopic than another form. The field is not advanced over the closest prior art with any new technical effect, since a non-hygroscopic form of mirtazapine was already available, which is the form of mirtazapine already available on the European market since 1995 (See for more details the reasoning and evidence addressed in paragraph 2.4). Simply providing a crystalline form of a compound in an alternative crystalline (anhydrous) form does not require inventive effort. A comparison with another anhydrate that is worse in properties than commercially available crystalline mirtazapine does not prove a new technical effect. Therefore claim 1 lacks inventive step.

2.2 Claim 2 defines a further characteristic of the anhydrate according to claim 1, that is, having not more than 0.5% water content. This characteristic does not have any technical effect and therefore cannot contribute to inventive step. Therefore claim 2 lacks inventive step as well.

2.3 Claims 3-6 claim the process of making the anhydrate of claim 1, but such methods as drying a hydrate, with heating, pulverization and reducing pressure are standard techniques for obtaining anhydrous compounds.
Therefore claims 3-7 lack inventive step.

2.4 Claim 7 defines crystals of mirtazapine hydrate.
This claim is not novel in view of:
a) D1
b) Prior use by the sale of dried, water containing mirtazapine prior to the earliest priority date claimed in the patent.

Concerning a)
D1 describes the purification of tritiated Org 3770 according to a method (pp 1066, lines 4-7) leading inevitably to tritiated Org 3770 hydrate, which is within the scope of claim 7. Org 3770 is a name for the chemical compound as defined in claim 7. Evidence for this is D2, which is from Scifinder, showing the names and chemical formula of mirtazapine/Org

3770. D3 and D4 show that the skilled person, working along the specific instructions in D1, will inevitably obtain mirtazapine hydrate according to claim 7.

Concerning b)

As clarified in paragraph 1, evidence is submitted that, before the earliest priority date of the patent, Organon has been selling dried, water-containing (2.5%) mirtazapine which falls within the scope of claim 7. Copies of invoices of product delivered to third parties will be produced and declarations are submitted confirming that this delivered product is made with methods which do not lead to any different product as can be characterized, as far as crystalline water-containing properties and X-ray diffraction patterns are concerned, than the mirtazapine product that has, since 1995, up to the present, been produced and sold by Organon. (See paragraph 1).

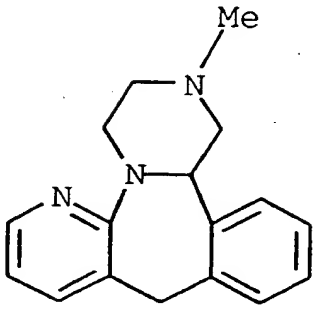
If patentee were to argue that the hydrate claimed in claim 7 is different from the mirtazapine made available by Organon, the claim would not involve an inventive step for reasons similar to those given for claim 1 in paragraph 2.1.

2.5 Claim 8 is not novel over D1. On page 1066 it is described that Org 3770 (=mirtazapine) is purified by crystallization from a water soluble organic solvent and water (p1066: methanol/water (1:1, v/v)).
Moreover, mirtazapine is a known compound. The crystallization method in claim 8 is a standard method for purifying a compound which are less soluble in water and soluble in a water miscible organic solvent. Therefore, no inventive step can be acknowledged for claim 8 either, in view of routine methods available to the skilled person.

2.6 Claims 9-11 are not defining further measures which would go beyond standard methods available to the skilled person.

Therefore, claims 1-11 define subject-matter that is not patentable according to the requirements of the EPC. It is requested that the opposition division revokes the patent in its entirety.

Registry Number: 85650-52-8



Formula: C17 H19 N3

CA Index Name: Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI)

Other Names: Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (±)-; 6-Azamianserin; Mepirzapin; Mepirzepine; Mirtazapine; Mirtazepine; Mirtazipine; Org 3770; Promyrtil; Remergil; Remergon; Remeron; Rexer; Zispin

-- Properties --

Property	Calculated Value	Condition	Note
Bioconc. Factor	1	pH 1	(1) ACD
Bioconc. Factor	1	pH 4	(1) ACD
Bioconc. Factor	3.55	pH 7	(1) ACD
Bioconc. Factor	21.3	pH 8	(1) ACD
Bioconc. Factor	47.4	pH 10	(1) ACD
Boiling Point	432.4±35.0 °C	Press: 760.0 Torr	(1) ACD
Enthalpy of Vap.	68.82±3.0 kJ/mol		(1) ACD
Flash Point	215.3±46.7 °C		(1) ACD
H acceptors	3		(1) ACD
H donors	0		(1) ACD
Koc	1	pH 1	(1) ACD
Koc	1	pH 4	(1) ACD

Koc	41.1	pH 7	(1) ACD
Koc	246	pH 8	(1) ACD
Koc	549	pH 10	(1) ACD
logD	-2.48	pH 1	(1) ACD
logD	-1.25	pH 4	(1) ACD
logD	1.38	pH 7	(1) ACD
logD	2.16	pH 8	(1) ACD
logD	2.51	pH 10	(1) ACD
logP	2.516±0.462		(1) ACD
Molar Solubility	Very Soluble	pH 1	(1) ACD
Molar Solubility	Very Soluble	pH 4	(1) ACD
Molar Solubility	Sparingly Soluble	pH 7	(1) ACD
Molar Solubility	Sparingly Soluble	pH 8	(1) ACD
Molar Solubility	Sparingly Soluble	pH 10	(1) ACD
Molecular Weight	265.35		(1) ACD
pKa	8.10±0.20	Most Basic	(1) ACD
Vapor Pressure	1.11E-7 Torr	Temp: 25.0 °C	(1) ACD

Notes:

(1) Calculated using Advanced Chemistry Development (ACD/Labs) Software Solaris V4.67 (© 1994-2004 ACD/Labs)

-- Resources --

References: ~405

STN Files: CAPLUS, ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK, MSDS-OHS, PHAR, PIRA, PROMT, RTECS, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

(Additional Information is available through STN International. Contact your information specialist, a local CAS representative, or the CAS Help Desk for Assistance)

Deleted Registry Number(s): 61337-67-5, 82601-27-2

AFFIDAVIT

I, Wilhelmus Petrus Hubertus Maria De Wildt

I declare the following:

I studied analytical chemistry at the Laboratory School in Arnhem and I passed the exams in 1987.

Since 1987 I am employed by N.V. Organon currently in the Department of Process Chemistry in Oss, The Netherlands.

I have read the patent EP 1225174 and in particular the claims 7-11, which, so I understand, are going to be subject in opposition proceedings before the European Patent Office.

I have purified mirtazapine with the method of crystallization from methanol/water as described according to (pp 1066, lines 4-7) of Kaspersen, Van Rooij, Sperling and Wieringa, J. Labelled Compounds and Radiopharmaceuticals Vol XXVII pp 1055-1068.

The following samples were prepared:
Experiment DW1785A
0,25 g mirtazapine (charge A48116) was dissolved in 1 ml methanol. 1 ml water was added dropwise at 20°C. While mirtazapine crystallized the mixture was stirred for 15 minutes at 20°C. Thereafter the crystals where collected by filtration and dried for 72 hours in vacuum at 20°C. Yield: 219 mg of sample A

Experiment DW1785B
0,25 g mirtazapine (charge A48116) was suspended in 0,5 ml methanol. The temperature of the mixture was increased to 55-60°C. (The compound dissolved at 35°C). Thereafter 0,5 ml water was added dropwise at 55-60°C. After addition of

the last amount of water crystallization started. The mixture was cooled to 20°C, filtered and dried for 72 hours in vacuum at 20°C. Yield 200 mg of sample B.

Experiment DW1785C
With 0,25 gram mirtazapine (charge A48116) the same procedure as in experiment A was followed, except that the crystalline mirtazapine was dried for 72 hours in a desiccator with sodium hydroxide as a drying agent. Yield 217 mg of sample C

This experimental work was done on November, 5 2004.

I passed the samples over to Peter van Hoof for further characterization.

William De Wildt Oss, 15 December 2004

AFFIDAVIT

I, Petrus Josef Cornelus Maria Van Hoof,

Declare the following:

I studied Chemistry at the university of Nijmegen and I passed the exams in 1993 and obtained a PhD in solid state chemistry in 1997.

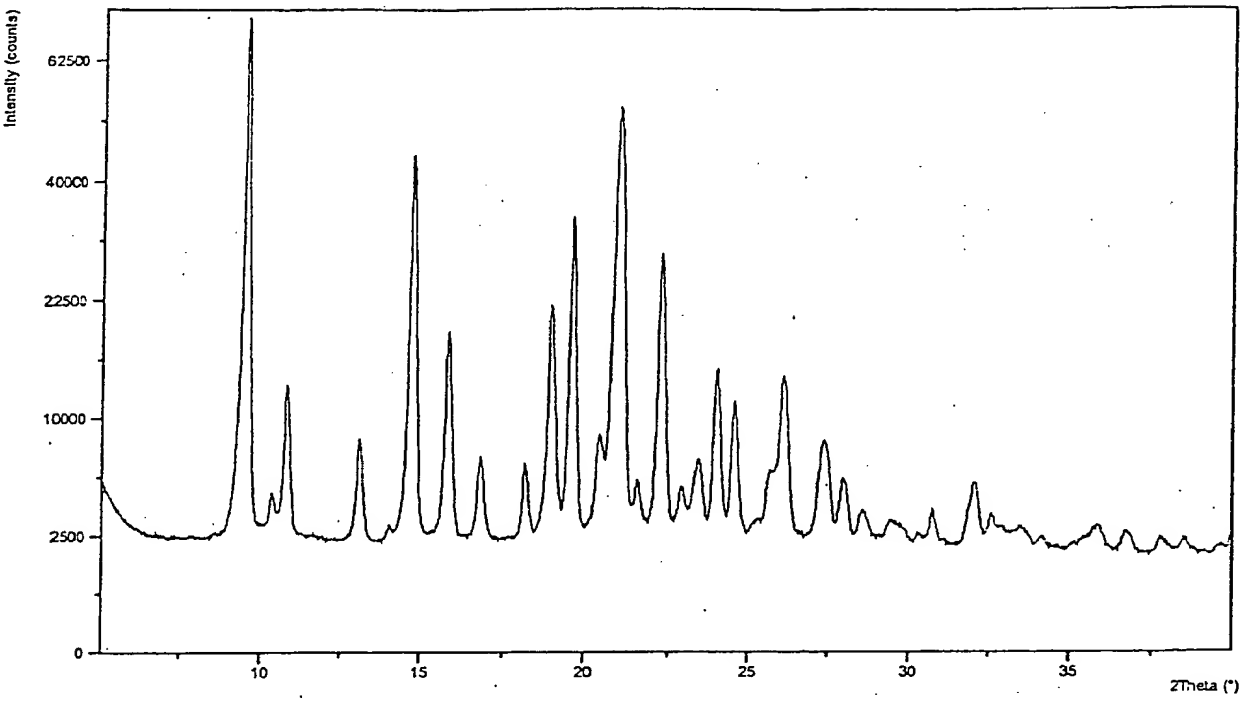
Since 1998 I am employed by N.V. Organon in the Department of Analytical Chemistry in Oss, The Netherlands.

I have read the patent EP 1225174 and in particular the claims 7-11, which, so I understand, are going to be subject in opposition proceedings before the European Patent Office.

I have measured X-ray powder diffraction patterns (using a Panalytical Xpert pro diffractometer) and water content using a Karl Fischer method of samples of purified mirtazapine as prepared by William De Wildt according to the method of crystallization from methanol/water as described (pp 1066, lines 4-7) by Kaspersen, Van Rooij, Sperling and Wieringa, J. Labelled, Compounds and Radiopharmaceuticals Vol XXVII pp 1055-1068.

My measurements are dated 10 November 2004 and show that the compound is a hydrate and that the compound has the same crystal structure as the mirtazapine hydrate described with XRPD in Fig 3 of EP 1225174 for use as starting material for a mirtazapine anhydrate. A representative XRPD of sample DW 1785A is attached to this declaration.

Peter van Hoof Oss, 16 December 2004


Intensity (counts)
62500
40000
22500
10000
2500
0
10
15
20
25
30
35
2Theta (°)

AFFIDAVIT

I, Catherine Mary Crowley

I declare the following:

I am educated as economist.

Since 1997 I am employed by N.V. Organon currently in the Department of Customer Relations in Oss, The Netherlands.

I have read the claims 7-11 of the patent EP 1225174, which, so I understand, are going to be subject in opposition proceedings before the European Patent Office.

I affirm that Remeron Tablets of strength 30 mg, identified as batch numbers or trace IDs 226533001, 226541001, 220284001, 237222001, 255668001, 270623001, 270162001 were delivered to clients during the year 1999. I retrieved this information from Organon's administrative systems. These systems prove to me that the indicated batch numbers were prepared with material obtained from Diosynth, which material was identified with batch numbers A21212001, A26199001, A25066001.

Catherine Crowley

Catherine Crowley Oss, 17 December 2004

AFFIDAVIT

I, Petrus Hubertus Gerardus Maria Kirchholtes

I declare the following:

I am educated as chemical engineer.

Since 1960 I am employed by Diosynth/Organon currently in the Department of R&D Chemistry in Oss, The Netherlands.

I have read the patent EP 1225174, which, so I understand, is going to be subject in opposition proceedings before the European Patent Office.

I affirm that I have inspected the manufacturing procedures identified with the following codes: DBV-3228, DBV-3331, DBV-3410, DHV-1664, DRV-94135, DRV-95113, SOP-467 and compared the differences with the manufacturing procedures identified as DBV-04487, DBV04299A, DBV04300, DBV04533, and which are currently in use.

I affirm that the changes are of such nature that these cannot have changed the physico-chemical properties, as far as the crystal structure or water content is concerned.

Peter Kirchholtes Oss 17 december 2004